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(54) Title: CATHEPSIN CYSTEINE PROTEASE INHIBITORS

(57) Abstract: This invention relates to a novel class of compounds which are cysteine protease inhibitors, including but not limited to, inhibitors of cathepsins K, L, S and B. These compounds are useful for treating diseases in which inhibition of bone resorption is indicated, such as osteoporosis.

TITLE OF THE INVENTION
CATHEPSIN CYSTEINE PROTEASE INHIBITORS

BACKGROUND OF THE INVENTION

A variety of disorders in humans and other mammals involve or are associated with abnormal bone resorption. Such disorders include, but are not limited to, osteoporosis, glucocorticoid induced osteoporosis, Paget's disease, abnormally increased bone turnover, periodontal disease, tooth loss, bone fractures, rheumatoid arthritis, osteoarthritis, periprosthetic osteolysis, osteogenesis imperfecta, metastatic bone disease, hypercalcemia of malignancy, and multiple myeloma. One of the most common of these disorders is osteoporosis, which in its most frequent manifestation occurs in postmenopausal women. Osteoporosis is a systemic skeletal disease characterized by a low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. Osteoporotic fractures are a major cause of morbidity and mortality in the elderly population. As many as 50% of women and a third of men will experience an osteoporotic fracture. A large segment of the older population already has low bone density and a high risk of fractures. There is a significant need to both prevent and treat osteoporosis and other conditions associated with bone resorption. Because osteoporosis, as well as other disorders associated with bone loss, are generally chronic conditions, it is believed that appropriate therapy will typically require chronic treatment.

Osteoporosis is characterized by progressive loss of bone architecture and mineralization leading to the loss in bone strength and an increased fracture rate. The skeleton is constantly being remodeled by a balance between osteoblasts that lay down new bone and osteoclasts that breakdown, or resorb, bone. In some disease conditions and advancing age the balance between bone formation and resorption is disrupted; bone is removed at a faster rate. Such a prolonged imbalance of resorption over formation leads to weaker bone structure and a higher risk of fractures.

Bone resorption is primarily performed by osteoclasts, which are multinuclear giant cells. Osteoclasts resorb bone by forming an initial cellular attachment to bone tissue, followed by the formation of an extracellular compartment or lacunae. The lacunae are maintained at a low pH by a proton-ATP pump. The acidified environment in the lacunae allows for initial demineralization of bone followed by the degradation of bone proteins or collagen by proteases such as cysteine

proteases. *See* Delaisse, J. M. *et al.*, 1980, *Biochem J* 192:365-368; Delaisse, J. *et al.*, 1984, *Biochem Biophys Res Commun* :441-447; Delaisse, J. M. *et al.*,1987, *Bone* 8:305-313, which are hereby incorporated by reference in their entirety. Collagen constitutes 95 % of the organic matrix of bone. Therefore, proteases involved in collagen degradation are an essential component of bone turnover, and as a consequence, the development and progression of osteoporosis.

Cathepsins belong to the papain superfamily of cysteine proteases. These proteases function in the normal physiological as well as pathological degradation of connective tissue. Cathepsins play a major role in intracellular protein degradation and turnover and remodeling. To date, a number of cathepsin have been identified and sequenced from a number of sources. These cathepsins are naturally found in a wide variety of tissues. For example, cathepsin B, F, H, L, K, S, W, and Z have been cloned. Cathepsin K (which is also known by the abbreviation cat K) is also known as cathepsin O and cathepsin O2. *See* PCT Application WO 96/13523, Khepri Pharmaceuticals, Inc., published May 9, 1996, which is hereby incorporated by reference in its entirety. Cathepsin L is implicated in normal lysosomal proteolysis as well as several disease states, including, but not limited to, metastasis of melanomas. Cathepsin S is implicated in Alzheimer's disease and certain autoimmune disorders, including, but not limited to juvenile onset diabetes, multiple sclerosis, pemphigus vulgaris, Graves' disease, myasthenia gravis, systemic lupus erythemotasus, rheumatoid arthritis and Hashimoto's thyroiditis; allergic disorders, including, but not limited to asthma; and allogenic immunbe responses, including, but not limited to, rejection of organ transplants or tissue grafts. Increased Cathepsin B levels and redistribution of the enzyme are found in tumors, suggesting a role in tumor invasion and matastasis. In addition, aberrant Cathpsin B activity is implicated in such disease states as rheumatoid arthritis, osteoarthritis, pneumocystisis carinii, acute pancreatitis, inflammatory airway disease and bone and joint disorders.

Cysteine protease inhibitors such as E-64 (*trans*-epoxysuccinyl-L-leucylamide-(4-guanidino) butane) are known to be effective in inhibiting bone resorption. *See* Delaisse, J. M. *et al.*, 1987, *Bone* 8:305-313, which is hereby incorporated by reference in its entirety. Recently, cathepsin K was cloned and found specifically expressed in osteoclasts *See* Tezuka, K. *et al.*, 1994, *J Biol Chem* 269:1106-1109; Shi, G. P. *et al.*,1995, *FEBS Lett* 357:129-134; Bromme, D. and Okamoto, K., 1995, *Biol Chem Hoppe Seyler* 376:379-384; Bromme, D. *et al.*, 1996, *J Biol Chem* 271:2126-2132; Drake, F. H. *et al.*, 1996, *J Biol Chem* 271:12511-

12516, which are hereby incorporated by reference in their entirety. Concurrent to the cloning, the autosomal recessive disorder, pycnodysostosis, characterized by an osteopetrotic phenotype with a decrease in bone resorption, was mapped to mutations present in the cathepsin K gene. To date, all mutations identified in the cathepsin K gene are known to result in inactive protein. *See* Gelb, B. D. *et al.*, 1996, *Science* 273:1236-1238; Johnson, M. R. *et al.*, 1996, *Genome Res* 6:1050-1055, which are hereby incorporated by reference in their entirety. Therefore, it appears that cathepsin K is involved in osteoclast mediated bone resorption.

Cathepsin K is synthesized as a 37 kDa pre-pro enzyme, which is localized to the lysosomal compartment and where it is presumably autoactivated to the mature 27 kDa enzyme at low pH. *See* McQueney, M. S. *et al.*, 1997, *J Biol Chem* 272:13955-13960; Littlewood-Evans, A. *et al.*, 1997, *Bone* 20:81-86, which are hereby incorporated by reference in their entirety. Cathepsin K is most closely related to cathepsin S having 56 % sequence identity at the amino acid level. The S_2P_2 substrate specificity of cathepsin K is similar to that of cathepsin S with a preference in the P1 and P2 positions for a positively charged residue such as arginine, and a hydrophobic residue such as phenylalanine or leucine, respectively. *See* Bromme, D. *et al.*, 1996, *J Biol Chem* 271: 2126-2132; Bossard, M. J. *et al.*,1996, *J Biol Chem* 271:12517-12524, which are hereby incorporated by reference in their entirety. Cathepsin K is active at a broad pH range with significant activity between pH 4-8, thus allowing for good catalytic activity in the resorption lacunae of osteoclasts where the pH is about 4-5.

Human type I collagen, the major collagen in bone is a good substrate for cathepsin K. *See* Kafienah, W., *et al.*, 1998, *Biochem J* 331:727-732, which is hereby incorporated by reference in its entirety. *In vitro* experiments using antisense oligonucleotides to cathepsin K, have shown diminished bone resorption *in vitro*, which is probably due to a reduction in translation of cathepsin K mRNA. *See* Inui, T., *et al.*, 1997, *J Biol Chem* 272:8109-8112, which is hereby incorporated by reference in its entirety. The crystal structure of cathepsin K has been resolved. *See* McGrath, M. E., *et al.*, 1997, *Nat Struct Biol* 4:105-109; Zhao, B., *et al.*, 1997, *Nat Struct Biol* 4: 109-11, which are hereby incorporated by reference in their entirety. Also, selective peptide based inhibitors of cathepsin K have been developed *See* Bromme, D., *et al.*, 1996, *Biochem J* 315:85-89; Thompson, S. K., *et al.*,1997, *Proc Natl Acad Sci U S A* 94:14249-14254, which are hereby incorporated by reference in their entirety. Accordingly, inhibitors of Cathepsin K can reduce bone resorption.

Such inhibitors would be useful in treating disorders involving bone resorption, such as osteoporosis.

Compounds of the instant invention are useful as inhibitors of cathepsins. Particularly, the compounds of the instant invention are useful as inhibitors of Cathepsins K, L, S and/or B. More particularly, the compounds of the instant invention are useful as inhibitors of Cathepsins K and/or L.

It is therefore an object of the invention to provide compounds which inhibit cathepsin activity in a mammal in need thereof.

It is another object of the invention to provide compounds which are useful for treating and/or preventing bone loss in a mammal in need thereof.

It is another object of the invention to provide compounds which are useful to reduce bone loss in a mammal in need thereof.

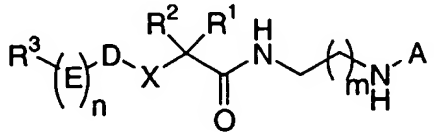
It is another object of the invention to provide compounds which are useful for treating and/or preventing bone fractures in a mammal in need thereof.

It is another object of the invention to provide compounds which are useful for treating and/or preventing osteoporosis in a mammal in need thereof.

It is another object of the invention to provide compounds which are useful for treating and/or preventing cathepsin dependent conditions or disease states in a mammal in need thereof.

SUMMARY OF THE INVENTION

The present invention relates to compounds of the following chemical formula:



wherein R^1 and R^2 are each independently selected from the group consisting of hydrogen and C_{1-6} alkyl; or R^1 and R^2 can be taken together with the carbon atom to which they are attached to form a C_{3-8} cycloalkyl ring wherein said 3-8 membered ring system may be optionally substituted with C_{1-6} alkyl and halo;

X is selected from the group consisting of NH, NR^4, $-NHSO_2-$, $-SO_2NH-$, O, $-C(R^5)(R^6)O-$, $-OC(R^5)(R^6)-$, S, SO_2, $-C(R^5)(R^6)S-$, $-SC(R^5)(R^6)-$, $C(R^5)(R^6)SO_2$, $SO_2C(R^5)(R^6)-$, $-C(R^5)(R^6)-$, $-C(R^5)(R^6)N(R^5)(R^6)-$, $-N(R^5)(R^6)C(R^5)(R^6)-$;

R^4 is C_{1-6} alkyl;

or R^4 and R^2 can be taken together with any of the atoms to which they may be attached or are between them to form a 4-8 membered ring system wherein said 4-8 membered ring system may be optionally substituted with C_{1-6} alkyl and halo;

R^5 and R^6 are each independently selected from the group consisting of hydrogen and C_{1-6} alkyl, wherein said alkyl group can be optionally substituted with one to three halo;

D and E are each independently selected from optionally substituted aryl, heteroaryl, C_{1-6} cycloalkyl and heterocycloalkyl wherein said aryl, heteroaryl, cycloalkyl and heterocycloalkyl may be optionally substituted with C_{1-6} alkyl and halo;

R^3 is selected from the group consisting of hydrogen, C_{1-6} alkyl, halo, aryl, heteroaryl, C_{1-6} cycloalkyl and heterocycloalkyl, wherein said alkyl, aryl, heteroaryl, C_{1-6} cycloalkyl and heterocycloalkyl can be optionally substituted with C_{1-6} alkyl and halo;

m is independently selected from an integer from one to five;

n is independently selected from an integer from zero to two;

A is selected from the group consisting optionally substituted aryl and heteroaryl;

and the pharmaceutically acceptable salts and N-oxide derivatives thereof.

The present invention also relates to pharmaceutical compositions comprising the compounds of the present invention and a pharmaceutically acceptable carrier.

The present invention also relates to methods for making the pharmaceutical compositions of the present invention.

The present invention also relates to methods of inhibiting cathepsin activity and/or treating cathepsin dependent conditions in a mammal in need thereof comprising administering to the mammal the compounds and pharmaceutical compositions of the present invention.

The present invention also relates to methods of treating, preventing and/or reducing bone loss in a mammal in need thereof comprising administering to the mammal the compounds and pharmaceutical compositions of the present invention.

The present invention also relates to methods of inhibiting treating and/or preventing osteoporosis in a mammal in need thereof comprising administering to the mammal the compounds and pharmaceutical compositions of the present invention.

The present invention also relates to methods of reducing bone loss in a mammal in need thereof comprising administering to the mammal the compounds and pharmaceutical compositions of the present invention.

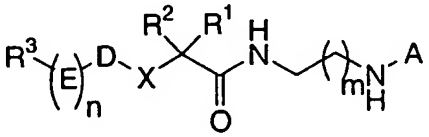
The present invention also relates to methods of treating and/or preventing bone fractures in a mammal in need thereof comprising administering to the mammal the compounds and pharmaceutical compositions of the present invention.

The present invention relates to the use of the compounds and pharmaceutical compositions of the present invention for the preparation of a medicament for treating or preventing bone loss in a mammal in need thereof.

The present invention relates to pharmaceutical compositions useful for treating or preventing bone loss in a mammal comprising a pharmaceutically effective amount of compounds of the present invention in association with pharmaceutically acceptable carriers.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to compounds of the following chemical formula:



wherein R^1 and R^2 are each independently selected from the group consisting of hydrogen and C_{1-6} alkyl; or R^1 and R^2 can be taken together with the carbon atom to which they are attached to form a C_{3-8} cycloalkyl ring wherein said 3-8 membered ring system may be optionally substituted with C_{1-6} alkyl and halo;

X is selected from the group consisting of NH, NR^4, $-NHSO_2-$, $-SO_2NH-$, O, $-C(R^5)(R^6)O-$, $-OC(R^5)(R^6)-$, S, SO_2, $-C(R^5)(R^6)S-$, $-SC(R^5)(R^6)-$, $C(R^5)(R^6)SO_2$, $SO_2C(R^5)(R^6)-$, $-C(R^5)(R^6)-$, $-C(R^5)(R^6)N(R^5)(R^6)-$, $-N(R^5)(R^6)C(R^5)(R^6)-$;

R^4 is C_{1-6} alkyl;

or R^4 and R^2 can be taken together with any of the atoms to which they may be attached or are between them to form a 4-8 membered ring system wherein said 4-8 membered ring system may be optionally substituted with C_{1-6} alkyl and halo;

R^5 and R^6 are each independently selected from the group consisting of hydrogen and C_{1-6} alkyl, wherein said alkyl group can be optionally substituted with one to three halo;

D and E are each independently selected from optionally substituted aryl, heteroaryl, C_{1-6} cycloalkyl and heterocycloalkyl wherein said aryl, heteroaryl, cycloalkyl and heterocycloalkyl may be optionally substituted with C_{1-6} alkyl and halo;

R^3 is selected from the group consisting of hydrogen, C_{1-6} alkyl, halo, aryl, heteroaryl, C_{1-6} cycloalkyl and heterocycloalkyl, wherein said alkyl, aryl, heteroaryl, C_{1-6} cycloalkyl and heterocycloalkyl can be optionally substituted with C_{1-6} alkyl and halo;

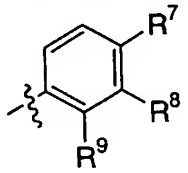
m is independently selected from an integer from one to five;

n is independently selected from an integer from zero to two;

A is selected from the group consisting optionally substituted aryl and heteroaryl;

and the pharmaceutically acceptable salts and N-oxide derivatives thereof.

In an embodiment of the invention, A is represented as

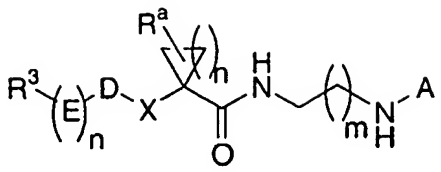


and R^7 , R^8 and R^9 are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, aryl-C_{1-6} alkoxy, C_{1-6} cycloalkoxy, C_{1-6} cycloalkyl-C_{1-6} alkoxy, heterocyclyoxy, heterocyclyl-C_{1-6} alkoxy, amino-C_{1-6} alkoxy and halo.

In an embodiment of the invention, X is NR^4 ; and R^4 and R^2 are taken together with any of the atoms to which they may be attached or are between them to form a 4-8 membered ring system wherein said 4-8 membered ring system may be optionally substituted with C_{1-6} alkyl and halo. In a further embodiment, X is NH. In another embodiment, X is S.

In an embodiment of the invention, D is selected from an optionally substituted 5-membered ring heteroaryl wherein said heteroaryl can be substituted with C_{1-6} alkyl, halo.

In another embodiment of the invention, the present invention relates to compounds of the formula:



X is selected from the group consisting of NH, NR^4, $-NHSO_2-$, $-SO_2NH-$, O, $-C(R^5)(R^6)O-$, $-OC(R^5)(R^6)-$, S, SO_2, $-C(R^5)(R^6)S-$, $-SC(R^5)(R^6)-$, $C(R^5)(R^6)SO_2$, $SO_2C(R^5)(R^6)-$, $-C(R^5)(R^6)-$, $-C(R^5)(R^6)N(R^5)(R^6)-$, $-N(R^5)(R^6)C(R^5)(R^6)-$;

R^4 is C_{1-6} alkyl;

or R^4 and R^2 can be taken together with any of the atoms to which they may be attached or are between them to form a 4-8 membered ring system wherein said 4-8 membered ring system may be optionally substituted with C_{1-6} alkyl and halo;

R^5 and R^6 are each independently selected from the group consisting of hydrogen and C_{1-6} alkyl, wherein said alkyl group can be optionally substituted with one to three halo;

D and E are each independently selected from optionally substituted aryl, heteroaryl, C_{1-6} cycloalkyl and heterocycloalkyl wherein said aryl, heteroaryl, cycloalkyl and heterocycloalkyl may be optionally substituted with C_{1-6} alkyl and halo;

R^3 is selected from the group consisting of hydrogen, C_{1-6} alkyl, halo, aryl, heteroaryl, C_{1-6} cycloalkyl and heterocycloalkyl, wherein said alkyl, aryl, heteroaryl, C_{1-6} cycloalkyl and heterocycloalkyl can be optionally substituted with C_{1-6} alkyl and halo;

R^a is selected from hydrogen, C_{1-6} alkyl and halo;

m is independently selected from an integer from one to five;

n is independently selected from an integer from one to five;

A is selected from the group consisting optionally substituted aryl and heteroaryl;

and the pharmaceutically acceptable salts and N-oxide derivatives thereof.

Specific embodiments of the present invention inlcude, but are not limited to (2*S*)-*N*-{2-[4-(benzyloxy)anilino]ethyl}-4-methyl-2-({4-[4-(1-piperazinyl)phenyl]-3-thienyl}amino)pentanamide and the pharmaceutically acceptable salts thereof.

An embodiment of the invention is a method of inhibiting cathepsin activity in a mammal in need thereof, comprising administering to the mammal a

therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above.

A class of the embodiment is the method wherein the cathepsin activity is cathepsin K activity.

Another embodiment of the invention is a method of treating or preventing cathepsin dependent conditions in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above.

A class of the embodiment is the method wherein the cathepsin activity is cathepsin K activity.

Another embodiment of the invention is a method of treating or preventing bone loss in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above.

Another embodiment of the invention is a method of reducing bone loss in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above.

Another embodiment of the invention is a method of treating or preventing bone fractures in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above.

Another embodiment of the invention is a method of treating or preventing osteoporosis in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the above pharmaceutical compositions described above.

Exemplifying the invention is a pharmaceutical composition comprising any of the compounds described above and a pharmaceutically acceptable carrier. Also exemplifying the invention is a pharmaceutical composition made by combining any of the compounds described above and a pharmaceutically acceptable carrier. An illustration of the invention is a process for making a pharmaceutical composition comprising combining any of the compounds described above and a pharmaceutically acceptable carrier.

Further exemplifying the invention is the use of any of the compounds described above in the preparation of a medicament for the treatment and/or

prevention of osteoporosis in a mammal in need thereof. Still further exemplifying the invention is the use of any of the compounds described above in the preparation of a medicament for the treatment and/or prevention of: bone loss, bone resorption, bone fractures, and/or disorders related to cathepsin functioning.

The present invention is also directed to combinations of any of the compounds or any of the pharmaceutical compositions described above with one or more agents useful in the prevention or treatment of osteoporosis. For example, the compounds of the instant invention may be effectively administered in combination with effective amounts of other agents such as an organic bisphosphonate or an estrogen receptor modulator. Nonlimiting examples of said organic bisphosphonates include alendronate, clodronate, etidronate, ibandronate, incadronate, minodronate, neridronate, risedronate, piridronate, pamidronate, tiludronate, zoledronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof. Preferred organic bisphosphonates include alendronate and pharmaceutically acceptable salts and mixtures thereof. Most preferred is alendronate monosodium trihydrate.

The precise dosage of the bisphosphonate will vary with the dosing schedule, the oral potency of the particular bisphosphonate chosen, the age, size, sex and condition of the mammal or human, the nature and severity of the disorder to be treated, and other relevant medical and physical factors. Thus, a precise pharmaceutically effective amount cannot be specified in advance and can be readily determined by the caregiver or clinician. Appropriate amounts can be determined by routine experimentation from animal models and human clinical studies. Generally, an appropriate amount of bisphosphonate is chosen to obtain a bone resorption inhibiting effect, i.e. a bone resorption inhibiting amount of the bisphosphonate is administered. For humans, an effective oral dose of bisphosphonate is typically from about 1.5 to about 6000 μg/kg body weight and preferably about 10 to about 2000 μg/kg of body weight.

For human oral compositions comprising alendronate, pharmaceutically acceptable salts thereof, or pharmaceutically acceptable derivatives thereof, a unit dosage typically comprises from about 8.75 mg to about 140 mg of the alendronate compound, on an alendronic acid active weight basis, i.e. on the basis of the corresponding acid.

For use in medicine, the salts of the compounds of this invention refer to non-toxic "pharmaceutically acceptable salts." Other salts may, however, be useful in the preparation of the compounds according to the invention or of their

pharmaceutically acceptable salts. When the compounds of the present invention contain a basic group, salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts which are generally prepared by reacting the free base with a suitable organic or inorganic acid. Representative salts include the following: acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, oleate, oxalate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, sulfate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide and valerate. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g., sodium or potassium salts; alkaline earth metal salts, e.g., calcium or magnesium salts; and salts formed with suitable organic ligands, e.g., quaternary ammonium salts.

The compounds of the present invention can have chiral centers and occur as racemates, racemic mixtures, diastereomeric mixtures, and as individual diastereomers, or enantiomers with all isomeric forms being included in the present invention. Therefore, where a compound is chiral, the separate enantiomers, substantially free of the other, are included within the scope of the invention; further included are all mixtures of the two enantiomers. Also included within the scope of the invention are polymorphs, hydrates and solvates of the compounds of the instant invention.

The present invention includes within its scope prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds of this invention which are readily convertible *in vivo* into the required compound. Thus, in the methods of treatment of the present invention, the term "administering" shall encompass the treatment of the various conditions described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound *in vivo* after administration to the patient. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of

Prodrugs," ed. H. Bundgaard, Elsevier, 1985, which is incorporated by reference herein in its entirety. Metabolites of these compounds include active species produced upon introduction of compounds of this invention into the biological milieu.

The term "therapeutically effective amount" shall mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by a researcher or clinician.

The term "bone resorption," as used herein, refers to the process by which osteoclasts degrade bone.

The term "alkyl" shall mean straight or branched chain alkanes of one to ten total carbon atoms, or any number within this range (i.e., methyl, ethyl, 1-propyl, 2-propyl, n-butyl, s-butyl, t-butyl, etc.).

The term "cycloalkyl" shall mean cyclic rings of alkanes of three to eight total carbon atoms, or any number within this range (i.e., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl).

The term "heterocycloalkyl," as used herein, shall mean a 3- to 8-membered fully saturated heterocyclic ring containing one or two heteroatoms chosen from N, O or S. Examples of cycloheteroalkyl groups include, but are not limited to piperidinyl, pyrrolidinyl, azetidinyl, morpholinyl, piperazinyl.

The term "aryl," as used herein, refers to a monocyclic or polycyclic system comprising at least one aromatic ring, wherein the monocylic or polycyclic system contains 0, 1, 2, 3, or 4 heteroatoms chosen from N, O, or S, and wherein the monocylic or polycylic system is either unsubstituted or substituted with one or more groups independently selected from hydrogen, halogen, C_{1-10} alkyl, C_{3-8} cycloalkyl, aryl, aryl C_{1-8} alkyl, amino, amino C_{1-8} alkyl, C_{1-3} acylamino, C_{1-3} acylamino C_{1-8} alkyl, C_{1-6} alkylamino, C_{1-6} alkylamino C_{1-8} alkyl, C_{1-6} dialkylamino, C_{1-6} dialkylamino-C_{1-8} alkyl, C_{1-4} alkoxy, C_{1-4} alkoxy C_{1-6} alkyl, hydroxycarbonyl, hydroxycarbonyl C_{1-6} alkyl, C_{1-5} alkoxycarbonyl, C_{1-3} alkoxycarbonyl C_{1-6} alkyl, hydroxycarbonyl C_{1-6} alkyloxy, hydroxy, hydroxy C_{1-6} alkyl, cyano, trifluoromethyl, oxo or C_{1-5} alkylcarbonyloxy. Examples of aryl include, but are not limited to, phenyl, naphthyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinolinyl, isoquinolinyl, benzofuranyl, benzothienyl, imidazolyl, benzimidazolyl, indolyl, thienyl, furyl, dihydrobenzofuryl, benzo(1,3) dioxolane, oxazolyl, isoxazolyl and thiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, tetrazolyl, triazolyl, oxadiazolyl, oxatriazolyl, thiadiazolyl, thiatriazolyl which are either unsubstituted or substituted with one or more groups independently selected from hydrogen, halogen, C_{1-10} alkyl,

C_{3-8} cycloalkyl, aryl, aryl C_{1-8} alkyl, amino, amino C_{1-8} alkyl, C_{1-3} acylamino, C_{1-3} acylamino C_{1-8} alkyl, C_{1-6} alkylamino, C_{1-6} alkylamino-C_{1-8} alkyl, C_{1-6} dialkylamino, C_{1-6} dialkylamino C_{1-8} alkyl, C_{1-4} alkoxy, C_{1-4} alkoxy C_{1-6} alkyl, hydroxycarbonyl, hydroxycarbonyl C_{1-6} alkyl, C_{1-5} alkoxycarbonyl, C_{1-3} alkoxycarbonyl C_{1-6} alkyl, hydroxycarbonyl C_{1-6} alkyloxy, hydroxy, hydroxy C_{1-6} alkyl, cyano, trifluoromethyl, oxo or C_{1-5} alkylcarbonyloxy. Preferably, the aryl group is unsubstituted, mono-, di-, tri- or tetra-substituted with one to four of the above-named substituents; more preferably, the aryl group is unsubstituted, mono-, di- or tri-substituted with one to three of the above-named substituents; most preferably, the aryl group is unsubstituted, mono- or di-substituted with one to two of the above-named substituents.

The term "heteroaryl," as used herein, shall refer to a system that includes an aryl portion, where aryl is as defined above, and one or two heteroatoms chosen from N, O or S.

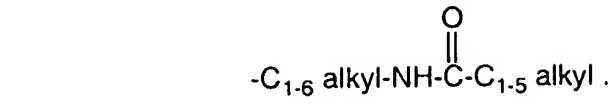
The term "halo" shall include iodo, bromo, chloro and fluoro.

Whenever the term "alkyl" or "aryl" or either of their prefix roots appear in a name of a substituent (e.g., aryl C_{0-8} alkyl) it shall be interpreted as including those limitations given above for "alkyl" and "aryl." Designated numbers of carbon atoms (e.g., C_{1-10}) shall refer independently to the number of carbon atoms in an alkyl or cyclic alkyl moiety or to the alkyl portion of a larger substituent in which alkyl appears as its prefix root.

In the compounds of the present invention, R^1 and R^2, when on the same carbon atom, can be taken together with the carbon atom to which they are attached to form a 3-8 membered ring wherein said 3-8 membered ring system may be optionally substituted with C_{1-6} alkyl and halo.

In the compounds of the present invention, R^4 and R^2 can be taken together with any of the atoms to which they may be attached or are between them to form a 4-8 membered ring system, wherein said 4-8 membered ring system may be optionally substituted with C_{1-6} alkyl and halo.

Under standard nonmenclature used throughout this disclosure, the terminal portion of the designated side chain is described first, followed by the adjacent functionality toward the point of attachment. For example, a C_{1-5} alkylcarbonylamino C_{1-6} alkyl substituent is equivalent to



$-C_{1-6}$ alkyl-NH-C-C_{1-5} alkyl .

In choosing compounds of the present invention, one of ordinary skill in the art will recognize that the various substituents, i.e. D, E, X, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^a, R^b, m and n are to be chosen in conformity with well-known principles of chemical structure connectivity.

The compounds of the present invention are available in racemic form or as individual enantiomers. It is generally preferable to administer the compounds of the present invention structure as enantiomerically pure formulations since most or all of the desired bioactivity resides with a single enantiomer. Racemic mixtures can be separated into their individual enantiomers by any of a number of conventional methods. These include chiral chromatography, derivatization with a chiral auxillary followed by separation by chromatography or crystallization, and fractional crystallization of diastereomeric salts.

The compounds of the present invention can be used in combination with other agents useful for treating cathepsin-mediated conditions. The individual components of such combinations can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. The instant invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly. It will be understood that the scope of combinations of the compounds of this invention with other agents useful for treating estrogen-mediated conditions includes in principle any combination with any pharmaceutical composition useful for treating disorders related to estrogen functioning.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The compounds of the present invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixers, tinctures, suspensions, syrups and emulsions. Likewise, they may also be administered in intravenous (bolus or infusion), intraperitoneal, topical (e.g., ocular eyedrop), subcutaneous,

intramuscular or transdermal (e.g., patch) form, all using forms well known to those of ordinary skill in the pharmaceutical arts.

The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician, veterinarian or clinician can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

Oral dosages of the present invention, when used for the indicated effects, will range between about 0.01 mg per kg of body weight per day (mg/kg/day) to about 100 mg/kg/day, preferably 0.01 to 10 mg/kg/day, and most preferably 0.1 to 5.0 mg/kg/day. For oral administration, the compositions are preferably provided in the form of tablets containing 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. A medicament typically contains from about 0.01 mg to about 500 mg of the active ingredient, preferably, from about 1 mg to about 100 mg of active ingredient. Intravenously, the most preferred doses will range from about 0.1 to about 10 mg/kg/minute during a constant rate infusion. Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, preferred compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittant throughout the dosage regimen.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as 'carrier' materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically

acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxy-ethylaspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polyactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and crosslinked or amphipathic block copolymers of hydrogels.

For purposes of this specification, the following abbreviations have the indicated meanings:

AcOH	=	acetic acid
Boc	=	t-butyloxycarbonyl
Boc_2O	=	di-tert-butyl dicarbonate

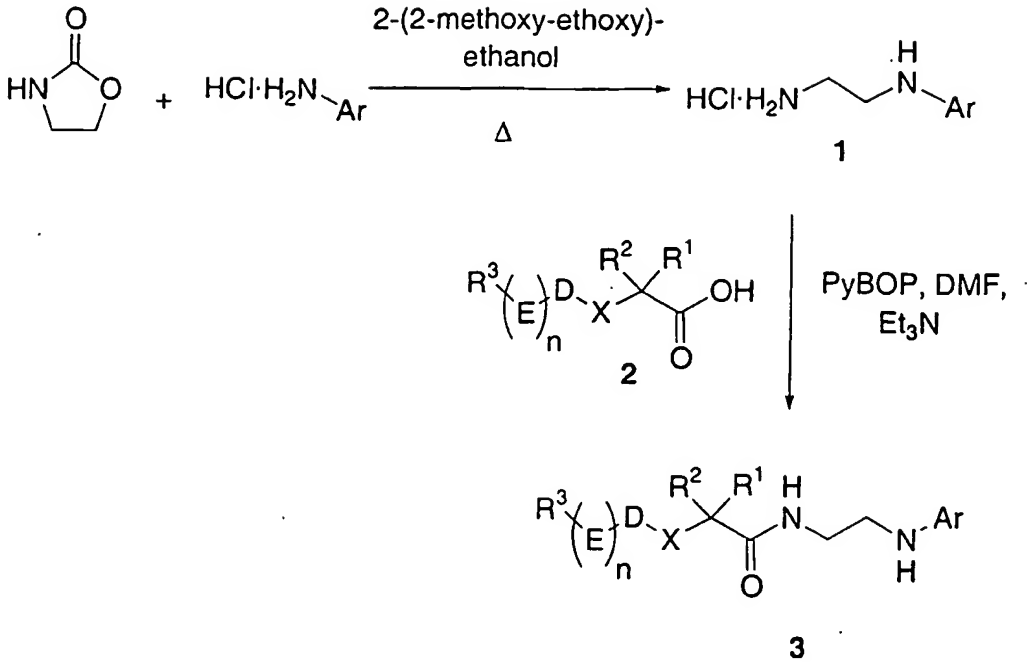
	BuLi	=	butyl lithium
	CCl_4	=	carbon tetrachloride
	CH_2Cl_2	=	methylene chloride
	CH_3CN	=	acetonitrile
5	$CHCl_3$	=	chloroform
	Cs_2CO_3	=	cesium carbonate
	CuI	=	copper iodide
	DMA	=	*N,N*-dimethyl acetamide
	DMAP	=	4-(dimethylamino)pyridine
10	DMF	=	N,N-dimethylformamide
	DMSO	=	dimethylsulfoxide
	EDCI	=	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
	Et_2O	=	diethyl ether
	Et_3N	=	triethylamine
15	EtOAc	=	ethyl acetate
	EtOH	=	ethanol
	HATU	=	o-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
	HOAc	=	acetic acid
20	K_2CO_3	=	potassium carbonate
	$KOBu^t$	=	potassium *tert*-butoxide
	LiOH	=	lithium hydroxide
	mCPBA	=	metachloroperbenzoic acid
	MeOH	=	methanol
25	$MeSO_3H$	=	methane sulfonic acid
	$MgSO_4$	=	magnesium sulfate
	Ms	=	methanesulfonyl = mesyl
	MsCl	=	methanesulfonyl chloride
	$NaBH_4$	=	sodium borohydride
30	NaH	=	sodium hydride
	Na_2CO_3	=	sodium carbonate
	$NaHCO_3$	=	sodium hydrogencarbonate
	NaOH	=	sodium hydroxide
	Na_2SO_4	=	sodium sulfate
35	NBS	=	N-bromosuccinimide

	NH_3	=	ammonia
	NH_4Cl	=	ammonium chloride
	Pd/C	=	palladium on carbon
	$PdCl_2(dppf)$	=	[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)
5	$Pd_2(dba)_3$	=	tris(dibenzylideneacetone)dipalladium(0)
	PPh_3	=	triphenylphosphine
	PPTS	=	pyridinium p-toluenesulfonate
	iPr_2Nli	=	lithium diisopropyl amide
	PyBOP	=	benzotriazol-1-yloxytris(pyrrolidino)phosphonium-
10			hexafluorophosphate
	rt	=	room temperature
	sat. aq.	=	saturated aqueous
	TFA	=	trifluoroacetic acid
	THF	=	tetrahydrofuran
15	tlc	=	thin layer chromatography
	Me	=	methyl
	Et	=	ethyl
	n-Pr	=	normal propyl
	i-Pr	=	isopropyl
20	n-Bu	=	normal butyl
	i-Bu	=	isobutyl
	s-Bu	=	secondary butyl
	t-Bu	=	tertiary butyl

25 The novel compounds of the present invention can be prepared according to the following general procedures using appropriate materials and are further exemplified by the following specific examples. The compounds illustrated in the examples are not, however, to be construed as forming the only genus that is considered as the invention. The following examples further illustrate details for the 30 preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds. All temperatures are degrees Celsius unless otherwise noted.

Compounds of the present invention can be prepared according to Scheme 1, as indicated below. The amine hydrochloride **1** can be coupled with the desired acid **2** to generate compound **3** of the present invention. The preparation of the 2-aminoethyl anilines **1** is as described in the literature (J. Org. Chem. **1992**, *57*, 6257).

Scheme 1



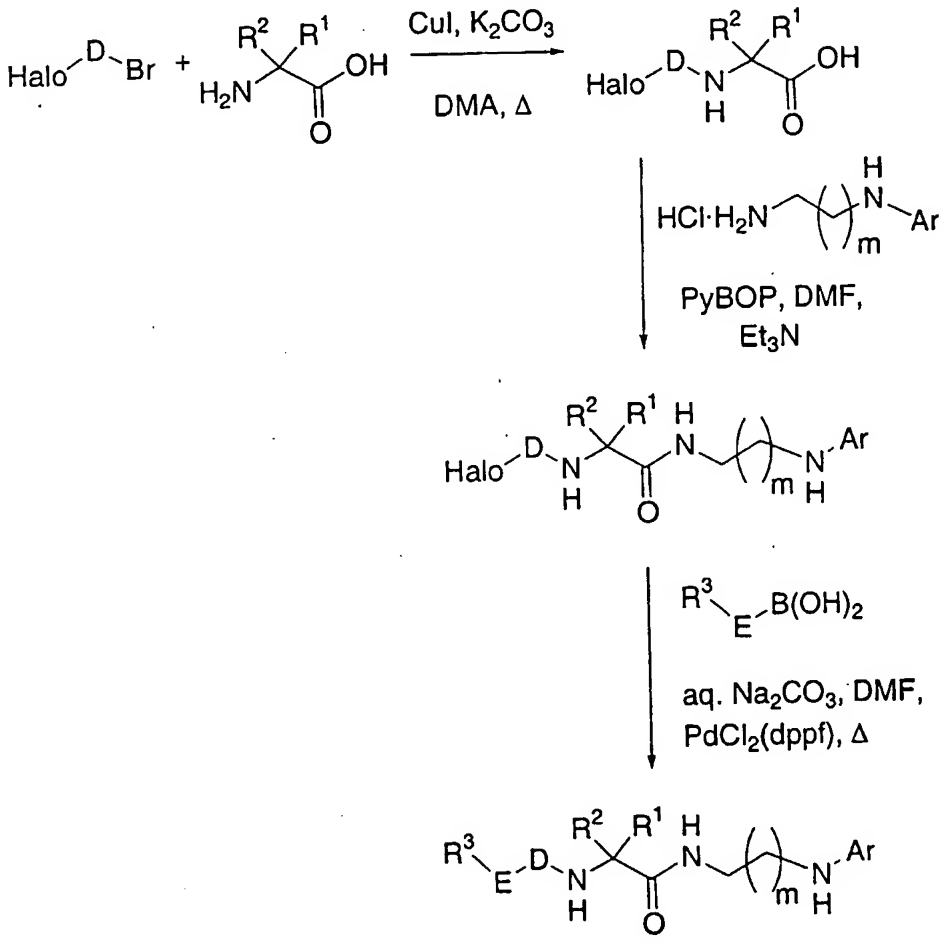
1

2

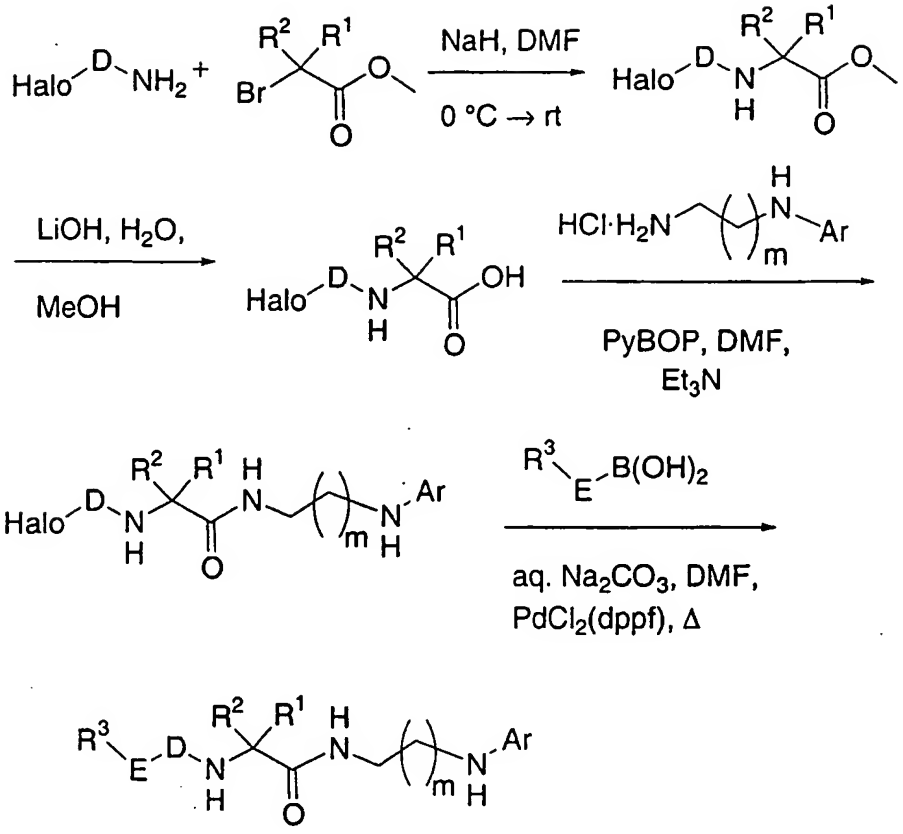
3

Compounds of the present invention in which X=NH can be prepared according to Scheme 2 or Scheme 3, as indicated below.

Scheme 2

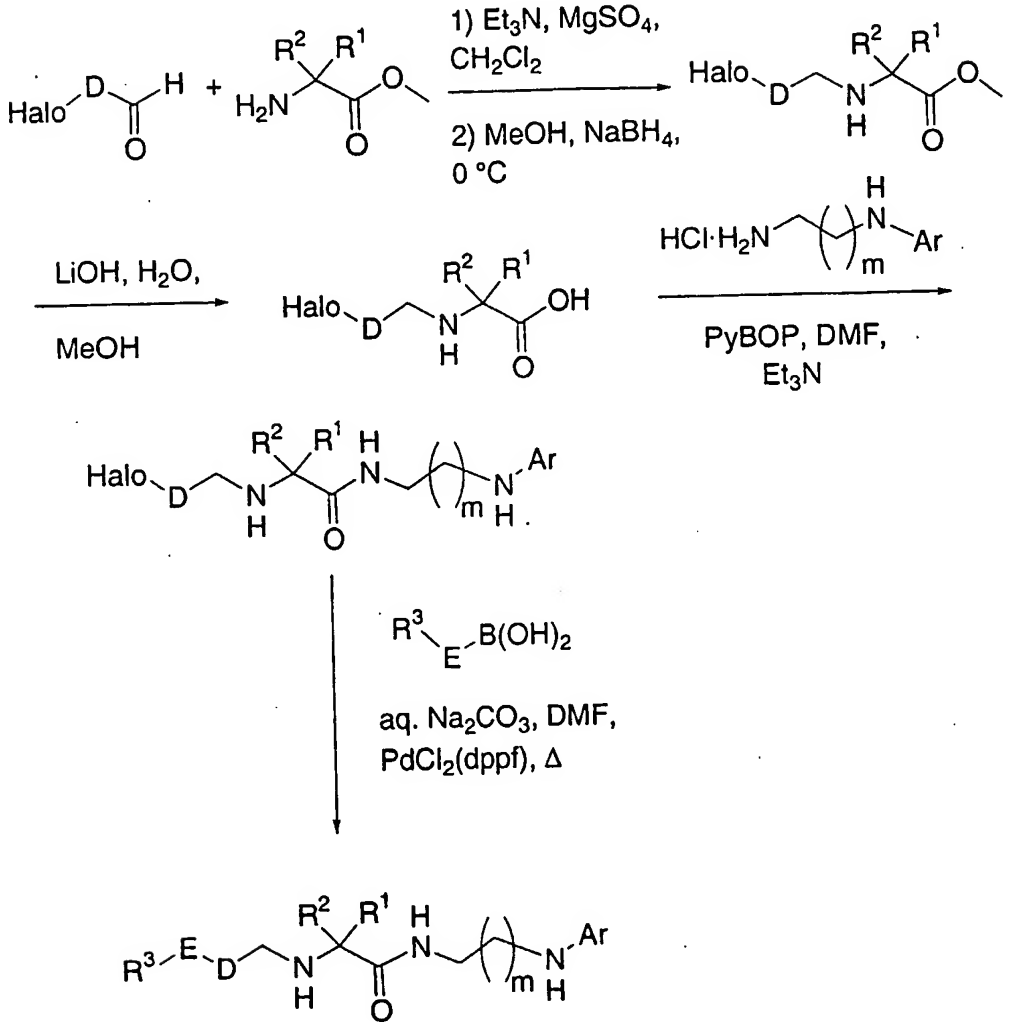


Scheme 3


Halo
D
NH2
+
R2
R1
Br
O
NaH, DMF
0 °C → rt
N
H
LiOH, H2O,
MeOH
OH
HCl·H2N
m
Ar
PyBOP, DMF,
Et3N
R3
E
B(OH)2
aq. Na2CO3, DMF,
PdCl2(dppf), Δ

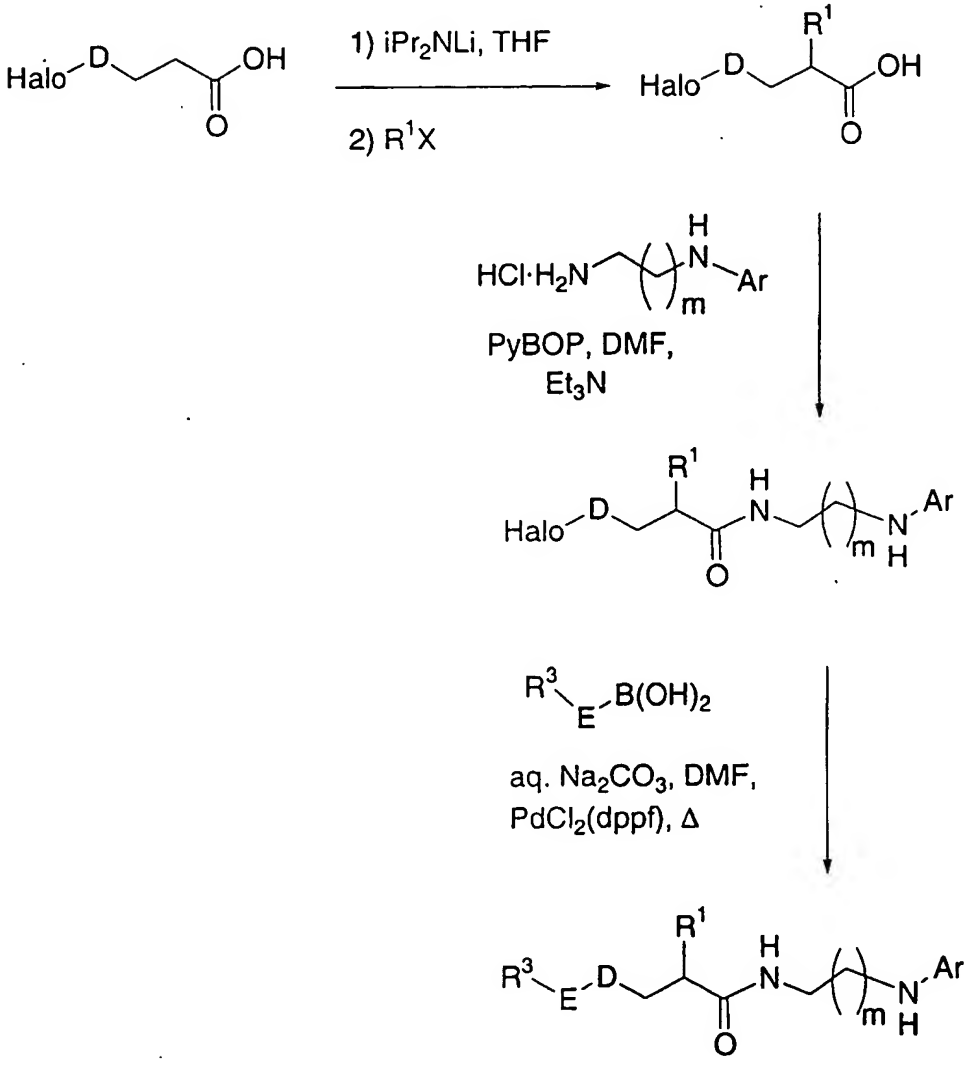
Compounds of the present invention in which X=CH_2NH can be prepared according to Scheme 4, as indicated below.

Scheme 4



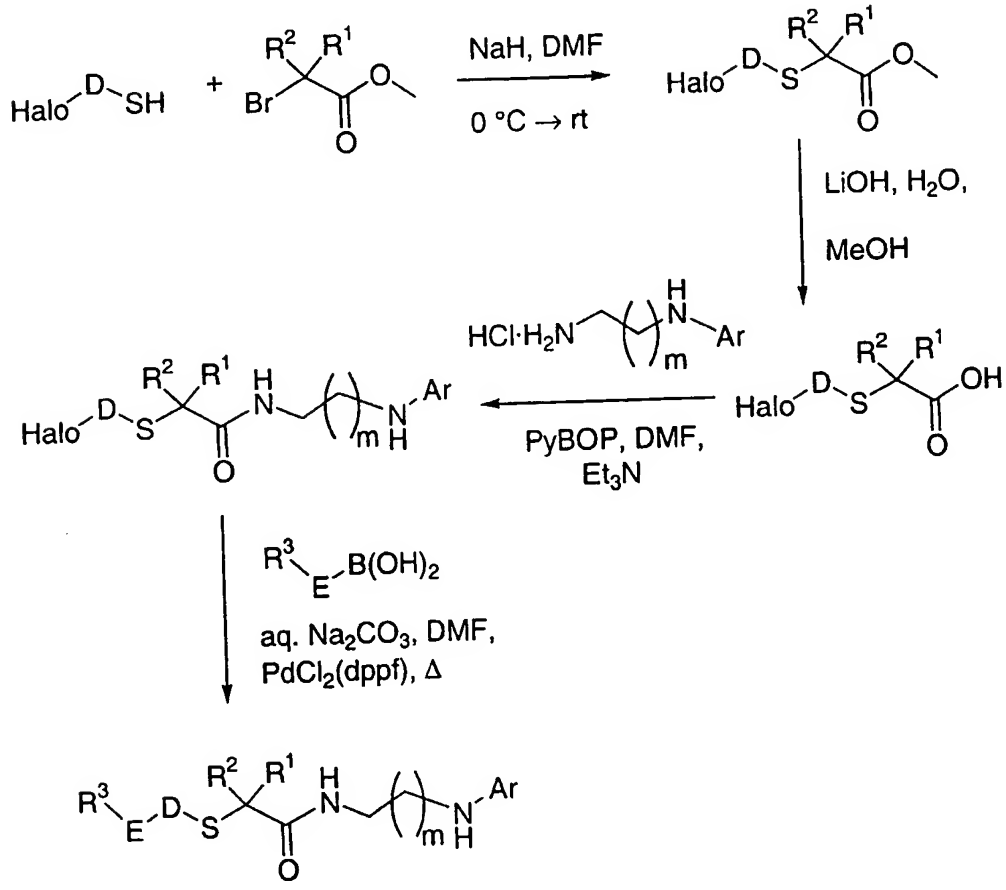
Compounds of the present invention in which $X=CH_2$ can be prepared according to Scheme 5, as indicated below.

Scheme 5



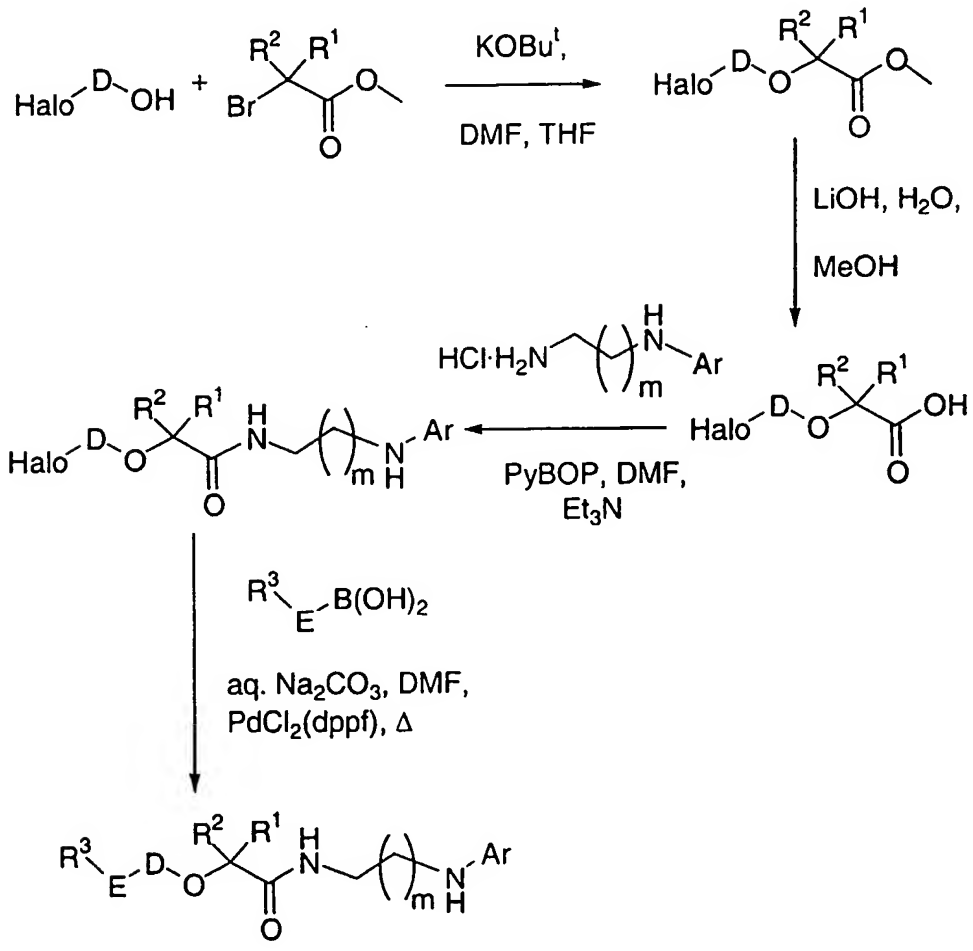
Compounds of the present invention in which X=S can be prepared according to Scheme 6, as indicated below.

Scheme 6



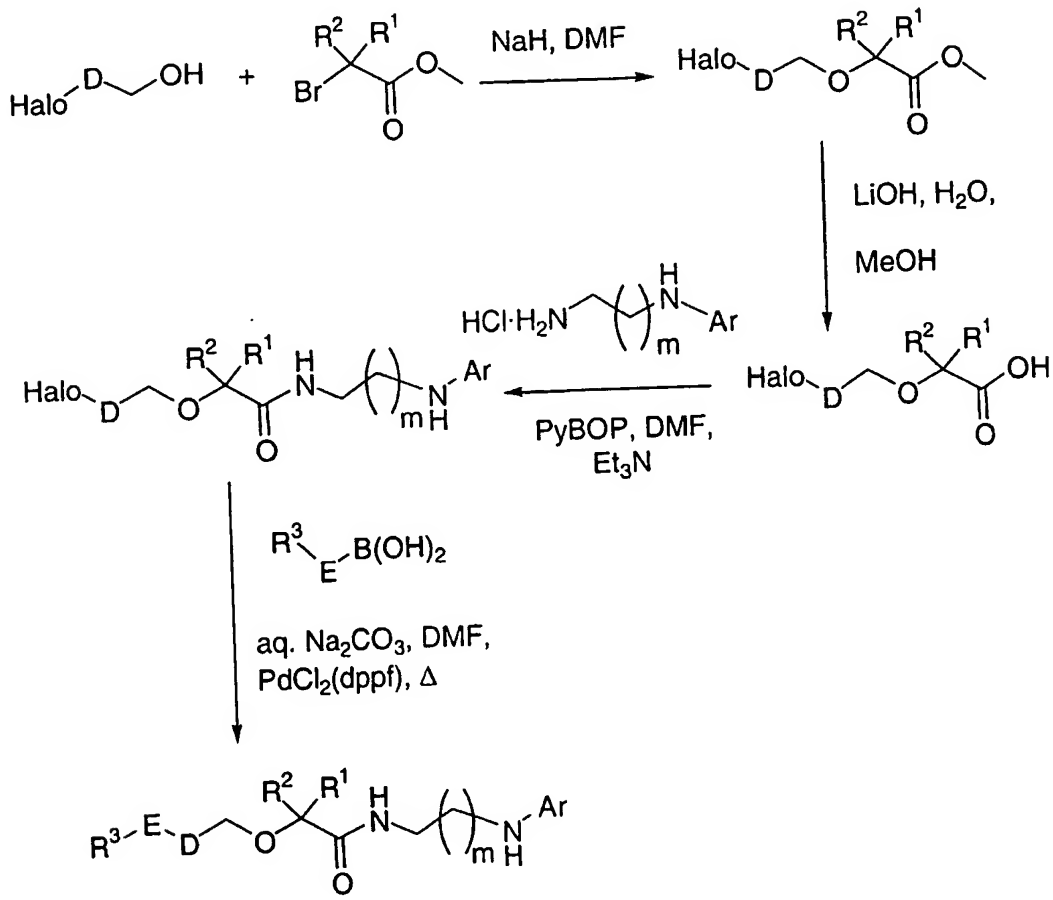
Compounds of the present invention in which X=O can be prepared according to Scheme 7, as indicated below.

Scheme 7



Compounds of the present invention in which X= CH_2O can be prepared according to Scheme 8, as indicated below.

Scheme 8



The following example describes the synthesis of a selected compound of the present invention.

The synthesis of (2*S*)-*N*-{2-[4-(benzyloxy)anilino]ethyl}-4-methyl-2-({4-[4-(1-piperazinyl)phenyl]-3-thienyl}amino)pentanamide in which X=NH is given below.

SYNTHESIS OF (2*S*)-*N*-{2-[4-(BENZYLOXY)ANILINO]ETHYL}-4-METHYL-2-({4-[4-(1-PIPERAZINYL)PHENYL]-3-THIENYL}AMINO)PENTANAMIDE

To 3,4-dibromothiophene (44.65 g, 184.55 mmol), L-leucine (16.14 g, 123.03 mmol), potassium carbonate (25.47 g, 184.55 mmol), and copper iodide (I) (3.52 g, 18.45 mmol) was added dry DMA (*N*,*N*-dimethylacetamide, 250 mL). The reaction flask was thoroughly degassed with dry nitrogen and heated at 95-100°C for 3 days. Water and hexane were added and the organic phase was separated and discarded (to remove excess 3,4-dibromothiophene). The aqueous phase was neutralized and the product was extracted with EtOAc (3X), dried over Na_2SO_4, concentrated *in vacuo*, and purified by flash chromatography over silica gel (EtOAc/Hex/AcOH, 1/1/1%) to afford (2*S*)-2-[(4-bromo-3-thienyl)amino]-4-methylpentanoic acid.

4-benzyloxyaniline hydrochloride (10g, 30.7 mmol) and 2-oxazolidone (2.7 g, 30.7 mmol) were mixed together in 11 ml of degassed ethoxyethoxyethanol . The suspension was heated at 165 °C. When the reaction mixture reached ~140 °C, the suspension turned into a solution. After 20h, the reaction mixture was allowed to cool to r.t. Upon cooling, a solid crashed out of solution. N^1-[4-(benzyloxy)phenyl]-1,2-ethanediamine hydrochloride, a brown solid was filtered off and used crude for the next step.

To (2*S*)-2-[(4-bromo-3-thienyl)amino]-4-methylpentanoic acid (215 mg, 0.736 mmol), PyBOP (425 mg, 0.810 mmol), N^1-[4-(benzyloxy)phenyl]-1,2-ethanediamine hydrochloride (455 mg, 1.62 mmol) in dry DMF (15 mL) under dry nitrogen was added triethylamine (350 µL, 2.51 mmol) dropwise and the reaction was stirred overnight. Aqueous sat. $NaHCO_3$ was added and the product extracted with Et_2O (2X), dried over Na_2SO_4, concentrated *in vacuo*, and purified by flash chromatography over silica gel (EtOAc/Hex, 4/6 then 1/1) to afford (2*S*)-*N*-{2-[4-(benzyloxy)anilino]ethyl}-2-[(4-bromo-3-thienyl)amino]-4-methylpentanamide.

To (2*S*)-*N*-{2-[4-(benzyloxy)anilino]ethyl}-2-[(4-bromo-3-thienyl)amino]-4-methylpentanamide (204 mg, 0.395 mmol) and 4-[4-(*tert*-butoxycarbonyl)-1-piperazinyl]phenylboronic acid (145 mg, 0.474 mmol) in DMF (10 mL) under dry nitrogen was added aqueous sodium carbonate (2M, 0.6 mL, 1.19 mmol) followed by the catalyst $PdCl_2$(dppf) (10 mg, 0.012 mmol). The reaction was heated to 85°C for 1 hour and more $PdCl_2$(dppf) (10 mg, 0.012 mmol) was added and

the reaction mixture was heated for an additional hour. Water was added and the product extracted with ether (2X), dried over Na_2SO_4, concentrated *in vacuo*, and purified by flash chromatography over silica gel (EtOAc/Hex, 45/55) to afford *tert*-butyl 4-{4-[4-({(1*S*)-1-[({2-[4-(benzyloxy)anilino]ethyl}amino)carbonyl]-3-methylbutyl}amino)-3-thienyl]phenyl}-1-piperazinecarboxylate).

To *tert*-butyl 4-{4-[4-({(1*S*)-1-[({2-[4-(benzyloxy)anilino]ethyl}amino)carbonyl]-3-methylbutyl}amino)-3-thienyl]phenyl}-1-piperazinecarboxylate (177 mg, 0.254 mmol) in dry THF (5 mL) under dry nitrogen was gradually added a total of 8 equivalents of $MeSO_3H$ (total of 12 µL, 1.31 mmol) over a period of 1 day in portions of 2 equivalents at a time. Aqueous sat. $NaHCO_3$ was added carefully and the product extracted with EtOAc (3X), dried over Na_2SO_4, concentrated *in vacuo*, and purified by flash chromatography over silica gel (NH_4OH/MeOH/CH_2Cl_2, 1.5/13.5/85) to afford (2*S*)-*N*-{2-[4-(benzyloxy)anilino]ethyl}-4-methyl-2-({4-[4-(1-piperazinyl)phenyl]-3-thienyl}amino)pentanamide.

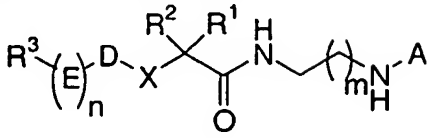
MS (+APCI): 598.6 $[M+H]^+$

Pharmaceutical Composition

As a specific embodiment of this invention, 100 mg of (2*S*)-*N*-{2-[4-(benzyloxy)anilino]ethyl}-4-methyl-2-({4-[4-(1-piperazinyl)phenyl]-3-thienyl}amino)pentanamide, is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size 0, hard-gelatin capsule.

WHAT IS CLAIMED IS:

1. A compound of the formula:



wherein R^1 and R^2 are each independently selected from the group consisting of hydrogen and C_{1-6} alkyl; or R^1 and R^2 can be taken together with the carbon atom to which they are attached to form a C_{3-8} cycloalkyl ring wherein said 3-8 membered ring system may be optionally substituted with C_{1-6} alkyl and halo;

X is selected from the group consisting of NH, NR^4, $-NHSO_2-$, $-SO_2NH-$, O, $-C(R^5)(R^6)O-$, $-OC(R^5)(R^6)-$, S, SO_2, $-C(R^5)(R^6)S-$, $-SC(R^5)(R^6)-$, $C(R^5)(R^6)SO_2$, $SO_2C(R^5)(R^6)-$, $-C(R^5)(R^6)-$, $-C(R^5)(R^6)N(R^5)(R^6)-$, $-N(R^5)(R^6)C(R^5)(R^6)-$;
R^4 is C_{1-6} alkyl;
or R^4 and R^2 can be taken together with any of the atoms to which they may be attached or are between them to form a 4-8 membered ring system wherein said 4-8 membered ring system may be optionally substituted with C_{1-6} alkyl and halo;

R^5 and R^6 are each independently selected from the group consisting of hydrogen and C_{1-6} alkyl, wherein said alkyl group can be optionally substituted with one to three halo;

D and E are each independently selected from optionally substituted aryl, heteroaryl, C_{1-6} cycloalkyl and heterocycloalkyl wherein said aryl, heteroaryl, cycloalkyl and heterocycloalkyl may be optionally substituted with C_{1-6} alkyl and halo;

R^3 is selected from the group consisting of hydrogen, C_{1-6} alkyl, halo, aryl, heteroaryl, C_{1-6} cycloalkyl and heterocycloalkyl, wherein said alkyl, aryl, heteroaryl, C_{1-6} cycloalkyl and heterocycloalkyl can be optionally substituted with C_{1-6} alkyl and halo;

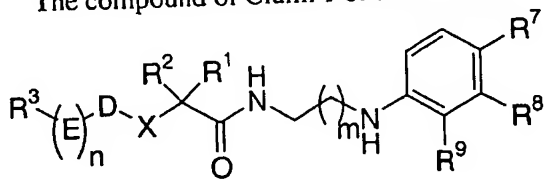
m is independently selected from an integer from one to five;

n is independently selected from an integer from zero to two;

A is selected from the group consisting optionally substituted aryl and heteroaryl;

and the pharmaceutically acceptable salts and N-oxide derivatives thereof.

2. The compound of Claim 1 of the formula:



wherein R^1 and R^2 are each independently selected from the group consisting of hydrogen and C_{1-6} alkyl; or R^1 and R^2 can be taken together with the carbon atom to which they are attached to form a C_{3-8} cycloalkyl ring wherein said 3-8 membered ring system may be optionally substituted with C_{1-6} alkyl and halo;

X is selected from the group consisting of NH, NR^4, $-NHSO_2-$, $-SO_2NH-$, O, $-C(R^5)(R^6)O-$, $-OC(R^5)(R^6)-$, S, SO_2, $-C(R^5)(R^6)S-$, $-SC(R^5)(R^6)-$, $C(R^5)(R^6)SO_2$, $SO_2C(R^5)(R^6)-$, $-C(R^5)(R^6)-$, $-C(R^5)(R^6)N(R^5)(R^6)-$, $-N(R^5)(R^6)C(R^5)(R^6)-$;

R^4 is C_{1-6} alkyl;

or R^4 and R^2 can be taken together with any of the atoms to which they may be attached or are between them to form a 4-8 membered ring system wherein said 4-8 membered ring system may be optionally substituted with C_{1-6} alkyl and halo;

R^5 and R^6 are each independently selected from the group consisting of hydrogen and C_{1-6} alkyl, wherein said alkyl group can be optionally substituted with one to three halo;

D and E are each independently selected from optionally substituted aryl, heteroaryl, C_{1-6} cycloalkyl and heterocycloalkyl wherein said aryl, heteroaryl, cycloalkyl and heterocycloalkyl may be optionally substituted with C_{1-6} alkyl and halo;

R^3 is selected from the group consisting of hydrogen, C_{1-6} alkyl, halo, aryl, heteroaryl, C_{1-6} cycloalkyl and heterocycloalkyl, wherein said alkyl, aryl, heteroaryl,

C_{1-6} cycloalkyl and heterocycloalkyl can be optionally substituted with C_{1-6} alkyl and halo;

R^7 , R^8 and R^9 are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, aryl-C_{1-6} alkoxy, C_{1-6} cycloalkoxy, C_{1-6} cycloalkyl-C_{1-6} alkoxy, heterocyclyoxy, heterocyclyl-C_{1-6} alkoxy, amino-C_{1-6} alkoxy and halo;

m is independently selected from an integer from one to five;

n is independently selected from an integer from zero to two;

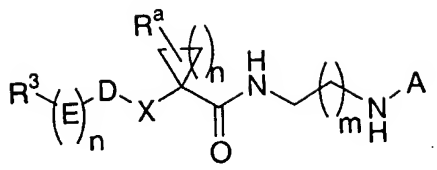
and the pharmaceutically acceptable salts and N-oxide derivatives thereof.

3. The compound of Claim 2 wherein X is NR^4 ; and R^4 and R^2 are taken together with any of the atoms to which they may be attached or are between them to form a 4-8 membered ring system wherein said 4-8 membered ring system may be optionally substituted with C_{1-6} alkyl and halo; and the pharmaceutically acceptable salts and N-oxide derivatives thereof.

4. The compound of Claim 3 wherein X is NH;
D is selected from an optionally substituted 5-membered ring heteroaryl wherein said heteroaryl can be substituted with C_{1-6} alkyl, halo;
E is selected from optionally substituted aryl, heteroaryl, C_{1-6} cycloalkyl and heterocycloalkyl wherein said aryl, heteroaryl, cycloalkyl and heterocycloalkyl can be substituted with C_{1-6} alkyl and halo;
and the pharmaceutically acceptable salts and N-oxide derivatives thereof.

5. The compound of Claim 2 wherein X is S, and the pharmaceutically acceptable salts and N-oxide derivatives thereof.

6. The compound of Claim 1 of the formula:



X is selected from the group consisting of NH, NR^4, $-NHSO_2-$, $-SO_2NH-$, O, $-C(R^5)(R^6)O-$, $-OC(R^5)(R^6)-$, S, SO_2, $-C(R^5)(R^6)S-$, $-SC(R^5)(R^6)-$, $C(R^5)(R^6)SO_2$, $SO_2C(R^5)(R^6)-$, $-C(R^5)(R^6)-$, $-C(R^5)(R^6)N(R^5)(R^6)-$, $-N(R^5)(R^6)C(R^5)(R^6)-$;

R^4 is C_{1-6} alkyl;

or R^4 and R^2 can be taken together with any of the atoms to which they may be attached or are between them to form a 4-8 membered ring system wherein said 4-8 membered ring system may be optionally substituted with C_{1-6} alkyl and halo;

R^5 and R^6 are each independently selected from the group consisting of hydrogen and C_{1-6} alkyl, wherein said alkyl group can be optionally substituted with one to three halo;

D and E are each independently selected from optionally substituted aryl, heteroaryl, C_{1-6} cycloalkyl and heterocycloalkyl wherein said aryl, heteroaryl, cycloalkyl and heterocycloalkyl may be optionally substituted with C_{1-6} alkyl and halo;

R^3 is selected from the group consisting of hydrogen, C_{1-6} alkyl, halo, aryl, heteroaryl, C_{1-6} cycloalkyl and heterocycloalkyl, wherein said alkyl, aryl, heteroaryl, C_{1-6} cycloalkyl and heterocycloalkyl can be optionally substituted with C_{1-6} alkyl and halo;

R^a is selected from hydrogen, C_{1-6} alkyl and halo;

m is independently selected from an integer from one to five;

n is independently selected from an integer from one to five;

A is selected from the group consisting optionally substituted aryl and heteroaryl;

and the pharmaceutically acceptable salts and N-oxide derivatives thereof.

7. (2S)-N-{2-[4-(benzyloxy)anilino]ethyl}-4-methyl-2-({4-[4-(1-piperazinyl)phenyl]-3-thienyl}amino)pentanamide and the pharmaceutically acceptable salts and N-oxide derivatives thereof.

8. A pharmaceutical composition comprising a compound according to any one of Claims 1 to 7 or a pharmaceutically acceptable salt or N-oxide derivative thereof and a pharmaceutically acceptable carrier.

9. A pharmaceutical composition made by combining a compound according to any one of Claims 1 to 7 or a pharmaceutically acceptable salt or N-oxide derivative thereof and a pharmaceutically acceptable carrier.

10. A process for making a pharmaceutical composition comprising combining a compound according to any one of Claims 1 to 7 or a pharmaceutically acceptable salt or N-oxide derivative thereof and a pharmaceutically acceptable carrier.

11. A method of inhibiting cathepsin activity in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of a compound according to Claim 1.

12. The method according to Claim 11 wherein the cathepsin activity is Cathepsin K activity.

13. A method of treating or preventing bone loss in a mammal in need thereof by administering to the mammal a therapeutically effective amount of a compound according to Claim 1.

14. A method of treating or preventing osteoporosis in a mammal in need thereof by administering to the mammal a therapeutically effective amount of a compound according to Claim 1.

15. A method of treating cathepsin dependent conditions in a mammal in need thereof by administering to the mammal a therapeutically effective amount of a compound according to Claim 1.

16. The use of a compound according to any one of Claims 1 to 7 or a pharmaceutically acceptable salt or N-oxide derivative thereof for the preparation of a medicament for treating or preventing bone loss in a mammal in need thereof.

17. A pharmaceutical composition useful for treating or preventing bone loss in a mammal comprising a pharmaceutically effective amount of a compound of any one of Claims 1 to 7 or a pharmaceutically acceptable salt or N-oxide derivative thereof in association with a pharmaceutically acceptable carrier.

18. A compound, salt or N-oxide, of any one of Claims 1 to 7 for use in inhibiting cathepsin activity in a mammal, treating or preventing bone loss or osteoporosis in a mammal, or treating a cathepsin dependent condition in a mammal.